Theories of Delusional Disorders : An Update and review

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Theories of Delusional Disorders

An Update and Review

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Abstract
Delusional syndromes can occur in a number of psychiatric, neurological or other disorders. They can also be caused by neurotoxic agents (e.g., heavy metals) as well as substance addiction. There are several hypotheses on the underlying cognitive or emotional processes associated with organic factors of delusional disorders, depending on the patient groups examined and the methods used. The aim of this paper is to provide a comprehensive review and critical assessment of the various, rather heterogeneous theories in this field.

Introduction

There is no generally accepted definition of delusion. This is remarkable – indeed, deplorable – not only because this phenomenon has been researched intensively ever since scientific discussion about psychiatric issues began some 200 years ago, but also because of the great clinical importance of delusions. In the pragmatic descriptions (not definitions) currently used worldwide, delusions often are classified as a pathological, incorrect assessment of reality which is unrelated to experience and adhered to with strong conviction despite evidence to the contrary and sufficient intelligence; i.e., the patient is incapable of learning. Equally important is the fact that these delusions are not shared by others of the patient's sociocultural background. At the same time, one must distinguish delusions from overvalued ideas, which have a strong emotional content and tend to polarize thinking but are still open to reason.

Acute delusions are accompanied by strong affect and exaggerated vigilance, a combination known as delusional mood. Fear, distrust and exaggerated vigilance cause the patient to read meanings into perfectly mundane events and even see them as related. Once these delusions are conceived, they are linked with the patient's emotions, motivations and background, instilled with meaning and built into his or her world of experiences, thus attaining a high degree of subjective certainty which places them beyond the reach of reason.

Clinical experience shows that acute delusions tend to become chronic. The patients systematize their delusions and incorporate them into their life. If delusions, especially persisting delusions, are elaborated upon through logical or paralogical thinking, they are called systematic delusions. Hence, chronic delusions are an integral part of the patients, constituting a part of their very thoughts, values, world view and goals. The contents usually relate to essential human experience and interaction: persecu-

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tion, harm and jealousy (e.g., the Othello syndrome in paranoia and in 'grumbler' delusions); love and sexuality (erotomania); personal greatness and glory (megalomania); guilt and failure (delusional depression) as well as the body (hypochondriac delusions). Special cases are the Capgras syndrome and its subform, the Fregoli delusion. Patients suffering from Capgras syndrome show a delusional belief that a person known to them is actually a double, and even see subtle differences between the original and the supposed double. In the case of the Fregoli delusion, patients believe that a family member or friend has taken on the appearance of a stranger, or that one family member has turned into another family member.

Delusional syndromes can occur in a number of psychiatric disorders, including schizophrenia, affective disorders, dementias, personality disorders and psychological disorders of organic origin. Despite the prominence of delusions in psychopathology, their etiology still is poorly understood. This article gives an overview of the principal current theories on the origin of delusional disorders, particularly models of organic brain dysfunction, together with a discussion of their potentials and limitations.

Organic Correlates of Delusion

Delusional Disorders of Organic Origin

Delusional syndromes can occur in a number of neurological and other disorders [1], including brain tumor, trauma to the skull and brain, cerebrovascular disorders, Huntington's chorea, epilepsy, infectious diseases affecting the central nervous system (e.g., HIV), endocrine disorders (e.g., hypothyroid disorder, impaired renal function) and autoimmune diseases (e.g., systemic lupus erythematosus). Delusional syndromes can also be caused by neurotoxic agents, such as heavy metals, and some recreational drugs. This led to the original assumption that organic factors could underlie delusional disorders.

Regarding the anatomical correlates of delusional disorders of organic origin, it was discovered early on that epileptic foci in the temporal limbic regions, especially in the left hemisphere, are associated with symptoms resembling schizophrenia [2]. Focal injury to the limbic system can also lead to delusions. The importance of left temporal lesions in these cases has been known for some time now [3]. Brain tumors, cerebrovascular disease and injury to the subcortical structures have also been associated with delusions [4]. Cummings [1, 5] postulated that paranoid syndromes are likelier to occur after limbic and subcortical trauma or dysfunction, and that there is a clear correlation with predominantly left-side injury, a hypothesis which already was proposed by Davison and Bagley [6]. The delusional contents were similar to those seen in delusional disorders without a clear organic cause. Thus, following an extensive study of case histories, it was possible to establish the existence of a Capgras syndrome in patients with systemic illness such as hepatic encephalopathy, vitamin B_{12} deficiency, hypothyroid disorder or diabetes mellitus. In the case of structural injury, Alexander et al. [7] thought that a combination of bilateral frontal and right temporal lesions played a significant role in the formation of a Capgras syndrome, whereas other authors thought lesions or dysfunctions in the right hemisphere to be more important [8–11]. To increase the intricacy of localization, Signer [12] emphasized the importance of frontal and temporal structures and summarized that lesions in the left temporal or right frontal areas are often associated with Capgras syndrome. Indeed, it may well be that patients showing delusions due to neurological and/or other somatic disorders may in fact constitute rather dramatic clinical cases, but not a truly representative group. Cummings [1, 5] pointed out that while it may not be possible to rule out the influence of pre-existing psychiatric illness or other predisposing factors (e.g., heredity, living conditions) from these cross-sectional samples, these factors had usually not been taken into account. Likewise, qualitative, quantitative and dynamic aspects of delusions or their development were hardly looked at. A prospective study by Cummings [1] revealed different clusters of delusional disorders which, depending on the severity and specificity of the neurological illness, ranged from simple delusions of persecution to reduplicative paramnesia and anosognosis, the latter associated with specific neurological disorders. In most of the 20 cases in this study, delusions decreased as cure of the underlying disorder progressed (as is also seen in delusions of organic origin).

Using carefully documented case histories of patients with organic illness or injuries to the brain, different models were proposed for delusional disorders of organic origin in the 1970's and 1980's. Delusions of patients with pronounced neuropsychological illness were looser and simpler, and often passing. Patients with complex and highly structured delusions, on the other hand, showed only slight cognitive impairment. This inverse correlation between neuropsychological impairment and the complexity of delusions may indicate that largely intact cognitive functions are an important prerequisite for elaborate delusional processing. Patients with Alzheimer's or multi-

infarct dementia affecting mainly the neocortical associative areas show simple delusions that are readily medicated. Complex delusions, on the other hand, tend to be seen in patients with extrapyramidal illness or with traumatic, neoplastic or cerebrovascular injury affecting mainly the subcortical areas (e.g., basal ganglia, thalamus) or the limbic system. Patients with lesions in these regions who show complex delusions are intellectually only slightly impaired: the delusions tend to become chronic and are largely resistant to treatment. Regarding lesions in the limbic system, laterality effects are important inasmuch as left-side injury tends to correlate with chronic schizophrenia-type disorders whereas right-side parietal temporal lesions are associated more with brief, sporadic hallucinatory and/or delusional episodes [4, 13]. It was also shown that lesions in the right hemisphere are involved in the formation of Capgras syndrome and reduplicative paramnesia [14].

These correlations between organic brain disorders, including structural injuries to certain brain regions, suggest that impaired brain function is likely to play a role in the pathogenesis of delusional disorders. Considering the neuropsychological functions of different brain structures, it becomes apparent that these regions, being part of complex neuronal regulatory cycles, are responsible for language- and perception-related as well as emotional processing [15]. It is believed that patients with a delusional syndrome (as in disorders of the limbic system) have unusual emotional experiences which are then made into delusions when interpreted by other, still intact regions of the brain. Hence, injury to subcortical areas like the basal ganglia is assumed to lead to specific dysfunctions of the neurotransmitter system, which in turn can lead to delusional syndromes via cognitive and emotional changes [1, 16]. In cortical dysfunction, right-side temporal parietal lesions are thought to lead to abnormal perception processes, which results in hallucinations and delusions due to deficient limbic processing. Conversely, focal left temporal injury is thought to impair limbic participation in linguistic processing, with possible development of delusional disorders [17].

These models are built on a great number of clinical observations showing that delusional disorders can arise from different injuries or dysfunctions of various brain regions. A feature common to all cases is impaired limbic cortical processing while a certain minimum of intellectual capacity is retained. Since not all patients with injury in these regions develop delusions, there must be further predisposing factors such as heredity, site and extent of the lesion, as well as premorbid personality traits. These additional factors could help to shed light on this issue, particularly the idiosyncratic content of delusional thinking and experiences. These aspects also are central to several other theories.

Findings of Imaging and Neurophysiological Studies

Although organic illness or injury to certain brain regions and delusional syndromes are often related, many delusional patients show no such lesions. Only a few of them have been examined using imaging methods such as single-photon emission computed tomography (SPECT), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) to locate functional correlates of their illness. A PET study on chronic schizophrenia patients [18] showed significant positive correlations between a global, reality perception-related complex of symptoms (including delusional experiences) and regional cerebral blow flood (rCBF) in the lateral prefrontal cortex, the ventral striatum and the temporal cortex (especially in the superior temporal gyrus and the parahippocampal regions). In a PET study on non-medicated schizophrenics, Kaplan et al. [19] found a correlation between left temporal rCBF activity patterns and the complex of reality perception-related symptoms. In a SPECT study of non-medicated schizophrenics, Ebmeier et al. [20] found negative activation effects in the left temporal striatum, but hyperactivation in the left striatum. A SPECT study by Sabri et al. [21] showed a significant correlation between the extent of delusional disorders and rCBF in the left frontal and the frontal medial regions. Although no data were given on the direction of causality for the correlations found (a common problem with correlation studies), the findings reported for the medial temporal and the ventral striatal regions of the limbic system are remarkable. Refining the methodology with multidimensional scaling to statistically calculate and plot the relative position of the regional activation patterns, it was possible to examine metabolic factors in delusional syndromes more precisely. In a SPECT study of delusional schizophrenic patients, Erkwoh et al. [22] found indices for a functional disconnectivity between frontal and temporal mesial limbic regions. Nevertheless, the correlations between rCBF parameters and quantified acute delusional-schizophrenic disorders were remarkably low. Interestingly, the strength of the correlations varied with the complexity of the schizophrenic symptoms (this in addition to delusional disorders). Nasrallah et al. [23] already reported a functional disconnectivity, although he associated a decreased interhemispheric information transfer with delusional disorders. An experimental cognitive study by

Romney and Mosley [24] also showed hemispheric processing deficits in paranoid schizophrenics.

Recent studies (also using MR voxel-based morphometry) show a correlation of delusional schizophrenic disorders with reduced gray matter in the left frontal lobe [25], impaired top-down support for overriding automatic responses in connection with dysfunctional activity of the left dorsolateral prefrontal cortex [26] as well as failure of the memory strategies associated with a functional disruption of dorsolateral prefrontal and temporal-limbic structures [27]. Regarding the delusional symptoms complex in particular, evidence has been mounting for dysfunctional connections between the frontal cortex, multimodal association areas and paralimbic structures, resulting in cognitive-perceptual-affective dissonance, which under specific conditions may cause delusions [28–32]. Examining paranoid schizophrenics, Ha et al. [33] found a significant reduction of gray matter in the left insular and the dorsolateral prefrontal regions, and bilaterally in the medial frontal, anterior cingulate, inferior frontal and superior temporal regions. On the other hand, patients showed significantly more gray matter in the bilateral cerebellum and the right striatum than did controls. Interestingly, there was a negative correlation between the severity score for 'lack of insight and judgment' and gray matter concentrations in the left posterior, the right anterior cingulate and bilateral inferior temporal regions, including the lateral fusiform gyri. In addition to the role of the frontal regulatory circuits, recent studies have shown an important role of the paralimbic structures in the pathophysiology of delusions and involvement of the perceptual and monitoring systems in the associate mechanism of insight.

Unlike the above-mentioned imaging methods, event-related potentials can provide precise data on early information processing as a biological marker. In schizophrenics, the auditory P300 amplitude of standard oddball discrimination tasks was reduced and delayed – mainly in the left temporal lobe, i.e., the posterior superior temporal gyrus with inconsistent volume reduction – and there was a correlation to enhanced global scores of positive symptoms as well as thought disorders, poor clinical outcome or negative symptoms [34–40]. Still, O'Donell et al. [41] found that in delusional patients, there was a particular correlation of the P300 amplitude and left posterior superior temporal gyrus volume. All together, the reductionist approach of a positive/negative dichotomy has led to some heterogeneous conclusions. Results of a more syndromal approach were findings of a smaller P300 in melancholic patients with psychotic features, i.e., hallucinations and/or delusions [42]. A recent study [43] found that patients with a delusional misidentification syndrome showed less excessive reduction of left prefrontal P300 amplitude but prolonged latency in the central midline region as opposed to schizophrenics without delusional misidentification syndrome. Generally, patients with a paranoid subtype of schizophrenia – characterized by delusions or hallucinations, absence of flat affect and disorganized speech or behavior, and little cognitive impairment – tend to show fewer reductions of cognitive event-related potentials than do undifferentiated schizophrenics. An impaired frontal processing negativity and mismatch negativity (P1, N1, P2, MMN) was mostly bilateral in paranoid but lateralized in non-paranoid schizophrenics, indicating that the paranoid patients retained a better preservation of the frontal-temporal dialogue in distinguishing relevant from irrelevant stimuli [44]. Together with better verbal skills, application of phonetical versus tonal stimuli leads to greater frontocentral N2 peaks with left-hemisphere dominance in paranoid schizophrenics [45]. However, disorders of the first stages of information processing (P2) and automatic categorization processing (N2) of non-target stimuli were also found to correlate specifically to hallucinations and delusions [37], which may indicate subtle early attentional deficits as an underlying factor.

Deficits in semantic processing (N400) point to abnormal activation of semantic networks with insufficient context utilization, but findings are inconsistent. Apart from preliminary data implying a lacking indirect priming effect in delusional patients without formal thought disorders [46], no systematic studies of delusions have been done so far.

Perry and Braff [47] also showed a correlation of delusions in schizophrenia and deficits in sensorimotor gating (measured using prepulse inhibition of the eye blink startle reflex). In a different paradigm, impaired prepulse inhibition was associated with greater delusions and suspicion only when following attended prepulse versus ignored prepulse [48], thus pointing to some basic anticipatory attentional modulations of delusional symptoms. Early sensory gating deficits with poorer P50 suppression were reported in subjects with more perceptual abnormalities and magical ideation [49]. A habituation deficit of the blink reflex also was found in depressive patients with delusions [50].

Mounting evidence of a thalamic-cortical imbalance in schizophrenia has led to research into high-frequency oscillations (possibly inhibitory in nature) of cortical somatosensory evoked potentials, which presumably are

generated in the afferent thalamocortical and early cortical fibers. Early high-frequency oscillations were absent in schizophrenia [51], and the higher amplitude in the low-frequency range showed a markedly inverse correlation to formal thought disorders and delusions [52]. Hence, delusional processing may also be caused by dysfunctional mechanisms of filtering and inhibition of irrelevant stimuli at the thalamic level before reaching the neocortex. Neurophysiological research may complement the morphopathometric methods, although this approach has not been pursued in great detail yet. We also can discern a parallel to neuropsychological research here.

Neuropsychological Findings

Since a variety of CNS and psychological disorders and delusions are related, it could well be that neuropsychological examinations will yield clues to subtle brain dysfunctions in delusional patients – regardless of the assumed etiology of the delusion. It is noteworthy that delusions are often associated with pronounced cognitive abnormalities [53]. It was expected that delusions would eventually correlate with specific impairments of cognitive processing (e.g., attentiveness, learning and memory, perception, planning, logical thinking), but research does not appear to support this hypothesis so far.

Maher [54] was one of the first to suspect neurocognitive dysfunctions in delusional patients. In his theory of 'perceptive-cognitive anomalies', he stressed a neuropsychological causality by assuming disorders of basic cognitive processing (e.g., losses in perception and attentiveness) to underlie delusional disorders. If filtering of stimuli (relevant versus irrelevant) is impaired, incoming stimuli will gain in complexity while losing coherence and consistency, thus leading to insecurity and disorientation in an environment which the patient perceives as first altered and then threatening. In order to alleviate the situation, the patient explains these changes by assigning them meanings and making connections. Delusional ideation and processing would thus be seen as the autochthonous conceptualization of an excessively complex, 'unconsciously' experienced altered perception. It remains unclear, however, to which group of patients Maher's data apply. More recent neuropsychological studies show that subjects with 'pure' delusions tend not to show any severe neuropsychological dysfunctions. Reviewing more than 32 neuropsychological articels, Zalewski et al. [55] found no great differences in cognitive performance between paranoid and non-paranoid schizophrenics. Furthermore, neuropsychological data are scarce for non-schizophrenic delusional patients, mainly because the disorder is rare and because patients usually do not see themselves as such, and so do not seek medical help or participate in scientific studies. Indeed, paranoid schizophrenics sometimes do better at executive functions, attentiveness, learning and memory tests. Nevertheless, many of the studies had methodological flaws, thus limiting their comparability; such as standardized, empirically validated tests not always being used for examining cognitive functions.

The study by Kremen et al. [56] is a case in point: performance for higher verbal (but not visual) memory was found to be associated with systematic, complex delusions, but these differences disappeared when comparing only paranoid with non-paranoid schizophrenics using the then current DSM-III-R criteria. Likewise, Bornstein et al. [57] found a higher fluidity of speech in paranoid than in non-paranoid and schizoaffective schizophrenics, but this difference also disappeared after controlling for group differences regarding education, medication and number of psychopathological symptoms. No group differences between paranoid and non-paranoid patients were found for expressive speech or language-related receptive abilities [58, 59]. An exception was the study by Langell et al. [60], who observed that delusional schizophrenics showed better language comprehension, expression and writing compared to non-paranoid schizophrenics. Kremen et al. [56] also found better language skills in patients with complex delusions, but these differences also disappeared when the data were re-analyzed according to DSM-III-R criteria (paranoid versus non-paranoid).

Unlike classical neuropsychological examinations, where individual cognitive functions are assessed, statistical classification studies [61–64] part from the usual criteria like DSM-III (i.e., paranoid versus non-paranoid) and instead classify groups according to neuropsychological test performance. Disregarding nosological boundaries has lately become very popular in psychiatric research. The above-mentioned studies yielded three subgroups: (1) a globally impaired group characterized by avolition, social withdrawal and blunted affect; (2) a group with slight cognitive disorders, characterized mainly by disorganized behavior and thinking (alogia, bizarre behavior, attentiveness and formal thought disorders), and (3) a neuropsychologically unremarkable group characterized solely by systematic delusions. The authors of these studies concluded that delusional disorders are associated only with slight cognitive impairments, if any. It was once again proposed that elaborate delusions require an intact neurocognitive system.

Summarizing the results of these neuropsychological studies, it appears that paranoid schizophrenics, in spite of their different cognitive style, show fewer neuropsychological disorders than do non-paranoid schizophrenics. So far, no indices for localizable cerebral dysfunctions in paranoid disorders have been found in neuropsychological studies, although the results are heterogeneous, probably at least in part due to different diagnostic criteria, the influence of medication, artifacts produced by spot sampling, as well as different neuropsychological tests. Regarding the problem of inclusion and exclusion criteria, Sorensen et al. [65] pointed out that these factors may artificially increase or decrease the number of paranoid or non-paranoid test subjects, thereby also skewing the test data for group comparisons. Bornstein et al. [57] also showed that between-group differences in cognitive performance could be due to confounding variables (see above). Finally, Kremen et al. [56] emphasized the importance of qualitative and quantitative aspects of delusions, an approach which seems promising, given that considering disorder-related characteristics across the various classifications had already been proposed by Bilder et al. [61] and Liddle et al. [63]. Even so, the neuropsychological correlates of delusion remain to be identified, especially in view of methodological problems. Assuming various levels of brain dysfunction in delusional disorders [66], the question also arises whether the neuropsychological examination methods currently used are not in fact too coarse to detect subtle organic brain changes or differences. Hypothesis-oriented research that takes into account the above-mentioned organic abnormalities of the brain seems more promising, although emotional or affective processing would have to be taken into consideration.

Neuronal Network Models

The neuronal network theory offers another explanation. According to this theory, delusions are seen as a complex activity pattern of neuronal networks which exhibit a special type of organization and are termed 'maps' (comparable to the somatosensory, motor, retinotopic and tonotopic brain centers). A central tenet of this theory is that these maps are plastic, i.e., they change over a person's life. This is taken from the neurosciences, which have conclusively proven the plasticity of the functional organization of the brain, as following amputations. The network theory was first advanced by Hoffman [67] to explain psychopathological syndromes, and later refined by Spitzer [68], particularly regarding delusions. Spitzer [68] assumes a connection between acute delusions and dopaminergic or noradrenergic hyperactivity. The mounting anxiety and insecurity which accompany acute delusions would thus go together with a neuromodulatory condition characterized by an increased noise-to-signal ratio in those neuronal networks responsible for the higher mental faculties. This would cause patients to focus more strongly on irrelevant events, increasing their subjective meaning. Once these meanings are activated in the semantic networks, they can influence subsequent perception and thinking, leading to delusional processing like ascribing meanings, starting relationships for no reason or being unable to judge different viewpoints critically. Acute delusions can then enter other higher-level cortical maps as input and there interact with experiences or other psychotically distorted ideas. The longer psychotic symptoms persist, the greater the likelihood of them altering the patient's personal attitudes or opinions. Hence, chronic delusions are understood as alterations of higher-level cortical map-like representational systems. Spitzer draws a parallel between Janzarik's [69] structural deformation which, neurobiologically speaking, would constitute a dynamic neuroplastic alteration. However, these alterations are also of therapeutic significance and Spitzer suggests different neuroleptic medication for acute or chronic delusions, depending on their noradrenergic and dopaminergic modulation. With chronic delusions, the altered maps require specific input, as through behavioral therapy. Behavioral therapy is also well suited because it simulates the effects of both classical and operational methods in network models [70]. It is therefore essential to create new experiences to counteract both emotional and cognitive processing. Although this theory seems very attractive, a new operationalization – and hence empirical validation – of this approach would be difficult. Unfortunately, research in this direction has not been pursued further.

Theories of Neurocognitive and Emotional Dysfunctions

Unlike the above-mentioned theories, the theory of mind, the probabilistic reasoning theory and the theory of attributional bias deal with neurocognitive abnormalities in delusional disorders and their organic correlates. Scientific study of the emotional aspects is only beginning. The following sections summarize the main aspects of these theories regarding organic correlates of brain dysfunction.

Theory of Mind

Gallese [71] proposed that the capacity to understand others as intentional agents could well be a basic organizational feature of our brain, enabling our rich and diversified intersubjective experiences. This perspective could be in a position to offer a global approach to the understanding of the vulnerability to major psychoses such as schizophrenia. On this note, the theory of mind (ToM) refers to the capacity of attributing mental states such as intentions, knowledge, beliefs, thinking and willing to oneself as well as to others. Amongst other things, this capacity allows us to predict the behavior of others. The ToM also includes the knowledge that the beliefs and desires of others may differ from our own. Central tenets of the ToM are beliefs, desires and actions. Together with our own beliefs and desires, our mental picture of reality leads us to decide on this or that course of action. However, the mental picture does not always correspond to actual reality. Meanwhile, there are now several fMRI studies which support the cortical correlates of the ToM. Frith [72] postulated that paranoid syndromes exhibit a specific ToM deficit, e.g., delusions of reference can be explained, at least in good part, by the patients' inability to put themselves in another person's place and thus correctly assess their behavior and intentions. Thought insertion and ideations of control by others can be traced back to dysfunctional monitoring of one's own intentions and actions. Hence, thoughts enter the patient's consciousness without his or her awareness of any intention to initiate these thoughts. The inability of these patients to correct errors is also believed to rest on an internal monitoring disorder. However, the question remains whether delusional ideas in a narrow sense and symptoms like thought insertion or other positive symptoms of schizophrenia should be discussed under the same perspective. Seen from this angle, serious neurophenomenological arguments against the global theory of meta-representational self-monitoring processing deficits in schizophrenic patients emerged [73, 74]. Nevertheless, Frith and Frith [75] found a particularly strong correlation of the medial and the lateral inferior prefrontal cortex and the temporal parietal transition brain regions with delusions and ToM deficits. Since deluded patients in symptomatic remission performed as well as normal controls at ToM tasks, ToM deficits seem to be a state rather than a trait variable [76]. Furthermore, the specificity of ToM deficits in delusions is also questionable because delusional patients may perform normally at ToM tasks [77]. Nevertheless, it is currently held that the medial prefrontal cortex is important for the perception of self [78] whereas the lateral frontal inferior cortex plays an important role – via mirror neurons – in planning and carrying out actions [79–81]. Psychological processes, on the other hand, are usually based on observations of the behavior of others, and seem to be connected with the superior temporal sulcus [82]. Another part of the 'social brain' circuitry which may be relevant in the context of ToM is the amygdala [83]. Recent work by Shaw et al. [84] suggests that lesions to the amygdala interfere with ToM reasoning most consistently if they were acquired relative early in life. This agrees with developmental theories of schizophrenia but the etiological relevance of ToM in delusional disorders is yet to be determined.

The Role of Emotions in Delusional Disorders

In addition to ToM deficits, the etiological relevance of which to delusions is increasingly being questioned, evidence has been mounting for some time now that emotional processes must be given special consideration, even if their exact role is not well understood yet [85]. Delusions driven by underlying affect (mood congruent) may differ neurocognitively from those which have no such connection (mood incongruent) [86]. Thus, specific 'delusion'-related autobiographical memory contents may be resistant to 'normal' forgetting processes, and so can escalate into continuous biased recall of mood-congruent memories and beliefs [86]. Regarding threat and aversive response, identification of emotionally weighted stimuli relevant to delusions of persecution has been associated with activation of the amygdala and the anterior insula [87]. Limbic-mediated inappropriate conjunction of affective tone to memories of imaginary events could impair reality monitoring and lead to delusions by adding misleading contextual information [88]. Seen in this context, it must also be kept in mind that schizophrenic patients show morphometric abnormalities of the amygdala, the thalamus, the hippocampus and the insula [89, 90], which by itself may indicate disorders such as affectively biased information processing. Interestingly, treatment of co-morbid mood disorders has been shown to reduce delusions [91]. The etiology of mood-incongruent delusions is less clear. It would therefore be good to take the role which emotions and affect play in delusions more into account.

Probabilistic Reasoning Bias

On the other hand, the theory of probabilistic reasoning bias [92] assumes that the probability-based decision-making process in delusional individuals requires less information than that of healthy individuals, causing them to jump to conclusions, a phenomenon which has been

confirmed by a number of studies [93]. This jumping to conclusions is neither a function of impulsive decision-making nor a consequence of memory deficit [94]. It has been suggested that the characteristic of delusional reasoning is the unwillingness to admit anything which would appear to refute one's beliefs [95]. However, Kemp et al. [96] pointed out that delusional patients are not deluded about everything and that there may be no global deficit in reasoning abilities. Goel et al. [97] found that healthy controls are most accurate on a syllogistic reasoning task, where they can mobilize their pre-existing beliefs, but not when the beliefs are irrelevant or emotive. On the other hand, schizophrenic patients were significantly less accurate at this task than controls in general. The authors assume that the excessive parallel mobilization of salient and irrelevant beliefs may be typical for dysfunctional reasoning processing in schizophrenic patients. Considering different underlying cerebral network processing, Goel and Dolan [98] showed that activation of the right lateral prefrontal cortex occurs when subjects inhibit responses associated with belief in order to reach the correct solution to a logical reasoning task, while the ventral medial prefrontal cortex is activated when reason is overruled by belief. Sanfey et al. [99] reported similar findings. One might hypothesize an imbalance in these neural processing systems in delusional patients, but taken together, the findings in reasoning abilities in delusional patients are only subtle and one might question the strength of their causality in delusional thinking.

Theory of Attributional Bias

In his theory of attributional style and self-discrepancies, Bentall [100, 101] and others proposed that negative events that could potentially threaten the self-esteem are attributed to others (externalized causal attribution) so as to avoid a discrepancy between the ideal self and the self as it is experienced. An extreme form of a self-serving attributional style should explain the formation of delusional beliefs, at least in cases where the delusional network is based on ideas of persecution, without any co-occurring perceptual or experiential anomaly. During the course of illness, the preferential encoding and recall of delusion-sensitive material can be assumed to continually reinforce and propagate the delusional belief [102]. Using psychophysiological methods, it could be shown that patients experiencing delusions of persecution were quick to identify the threatening elements in 'ambiguous' pictures but, rather counter-intuitively, actually spent less time reappraising these threatening elements than did controls without delusions of persecution [103]. Patients may also expect a threat where none exists.

Blackwood et al. [104] found that non-self-serving attributional bias is associated with activity in the left precentral gyrus, a region which is thought to play an important role in the executive control of behavior inhibition [105] as well as in semantic memory representation. The authors believe that in delusional patients, self-serving attributional bias is mainly a motivationally prepotent response, with the corresponding activity in the precentral gyrus representing the inhibitory process necessary for this particular attributional bias. However, Blackwood et al. [102] point out that those brain regions where delusional patients show remarkable cognitive activation are largely those which correlate with the extent of delusional disorders in other patients. Furthermore, these are also the regions where paranoid schizophrenic patients show structural [106, 107] and functional abnormalities [108]. Particularly in the case of paranoia and the sociocognitive dysfunctions thought to be associated with it, Blackwood et al. [102] believe that the amygdala and the ventral medial prefrontal cortex are also involved. Their assumption is based on the fact that the amygdala plays a significant role in encoding and recall of emotionally and socially relevant clues such as facial expression [109], something which could be observed in many patients with lesions in this region. The ventral medial prefrontal cortex, on the other hand, is thought to play an important role in assessing social situations regarding their emotional and social significance to the individual, according to Damasio's theory of the self [110]. Taken together, hypoactivation would characterize the delusional state, reflecting excessive attention to self-referential information with a diminished capability to inhibit the self-serving attributional bias.

Recent work with fMRI [111] has shown that when delusional patients evaluate potentially negative personal statements, they show less activation of the rostral-ventral anterior cingulate cortex – a region noted for self-monitoring – yet show greater activation in the posterior cingulate gyrus than do normal controls. The authors suggest that this underlies impaired self-reflection in delusional states involving ideas of persecution. Here, too, the etiological relevance of this approach is questionable.

Nevertheless, research of the cerebral correlates of attentiveness distortion or shifting in the sense of attentional bias regarding neutral or threatening stimuli has shown that these activate a specific neuronal network which includes the left lateral inferior frontal cortex, the ventral striatum and the anterior cingulate, the left lateral inferior frontal cortex handling semantic processing [112], the

ventral striatum contributes to the egocentric memory [113], and anterior sections of the cingulate cortex to the motivational content of stimuli [114]. Further support for a neurobiological contribution to the development of delusions has recently been reported. Zwanzger et al. [115] attempted to treat depression in a patient using repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex. After several sessions, the patient developed severe psychotic symptoms with ideas of persecution – which he had never had before. These disappeared when rTMS was combined with medication. Interestingly, it was recently shown that acute rTMS has a dopaminergic action in healthy volunteers [116]. Future work may clarify whether alteration or amelioration of perceptual input in 'perceptual' delusions can attenuate delusional belief. Hoffman et al. [117] have recently shown that auditory hallucinations can be greatly reduced by slow (1-Hz) TMS stimulation of the inferior temporal lobe, which is adjacent to the primary auditory cortex.

Summary

The data available on neurobiological, cognitive and neuropsychological correlates of delusions suggest dysfunctions of the prefrontal, limbic and subcortical regions, but further research is needed. Still, a neurobiologically sound and empirically validated theory of delusions is not in sight, although recent examination methods are better at detecting abnormal brain structures or connectivities. However, a simple model assuming purely organic causes is not enough since delusions can occur without any detectable brain disorder. Neurobiological factors are only a venue through which psychological processes operate and, regarding delusions, counterbalance belief structures. Delusional disorders are likely to be caused by a combination of neurobiological, cognitive and other psychological factors. It is no surprise, therefore, to find different contending hypotheses and the data somewhat inconsistent, even contradictory. The competing approaches are good inasmuch as each sheds light on a different aspect of delusional symptoms, aspects for which a unified theory may perhaps be developed in the future. In closing, it should be pointed out that, to a greater or a lesser extent, all the neurobiological, psychological and neuropsychological approaches listed here stress cognition, yet the specific interaction between emotional and cognitive areas has hardly been investigated, which is surprising since delusions have a strong emotional component. Research on delusion always was and always will be at the center of psychiatric conceptualization. It is very unlikely that this complex phenomenon – and paranoid and schizophrenic psychoses in general – will be traced back to one single cause. The fact that patients can very well 'overcome' their delusions could indicate that these are not quite so fixed and immobile and that there may be subgroups with different etiologies, although we are only beginning to understand them.

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